

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-909

CHEMISTRY REVIEW(S)

ALLEGRA ODT
(fexofenadine HCl)
NDA 21-909

**Summary of the Basis for the Recommended Action
from Chemistry, Manufacturing, and Controls**

Applicant: Sanofi Aventis
200 Crossing Boulevard, PO Box 6890
Bridgewater, NJ 08807

Indication: Treatment of seasonal allergic rhinitis and for treatment of chronic idiopathic urticaria in children 6 to 11 years of age.

Presentation: Immediate release, orally disintegrating tablet (ODT) intended for twice-a-day oral dosing. Each is a white, flat-faced, 1/2-in round-shaped tablet that is debossed with a scripted "e" symbol on one side and "311AV" on the other side. The total tablet weight is _____ Tablets are supplied individually in blisters, 6-count cards, and packaged into cartons of 10.

b(4)

EER Status: Acceptable 2-NOV-2006

Consults: DMETS - Acceptable 21-MAR-2007
EA - FONSI 29-APR-2007

Original Submission: 28-SEP-2006

Post-Approval Agreements:

The sponsor agrees to introduce _____ of finished batches, or _____ batches (whichever is greater), into the approved stability protocol for the first two years. Subsequently, _____ batch will be introduced annually.

b(4)

Drug Substance:

Fexofenadine hydrochloride is non-sedating, long-acting anti-histamine with selective peripheral histamine H1-receptor antagonist activity. According to the labeling, this compound is a white crystalline powder that is soluble in methanol and poorly soluble in water. Both enantiomers are equipotent. The Biopharmaceutics Classification System places this compound in the low solubility/low permeability category. No new information on drug substance is provided in this NDA.

All chemistry information on the drug substance is provided by cross-reference to NDA 20-625 for Allegra Capsules (approved 7/25/96) from the same sponsor, Sanofi-Aventis, and all subsequent supplements and annual reports made thereto.

Although there are two approved manufacturers, only drug substance manufactured at Aventis' Frankfurt, Germany facility will be used for the ODT product. There is no USP monograph. Other applications, NDA 20-872 (approved 2/25/00) for Allegra Tablets, NDA 21-963 (approved 10/16/06) for Allegra Oral Suspension, and the Allegra-D formulations (NDA 21-704 and NDA 20-786), all from the same sponsor, Sanofi-Aventis, also use the same drug substance with the same controls.

Conclusion: Drug substance is acceptable.

Drug Product:

The drug product orally disintegrating tablets are manufactured at CIMA LABS INC.'s facility in Eden Prairie, MN, using their proprietary OraSolv® technology. Due to its bitter taste, the active ingredient is taste-masked inside the ~~_____~~ and released in the stomach at acid pH. Flavorings and sweetener are added to make the disintegrating tablet pleasant tasting.

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:
i

b(4)

b(4)

b(4)

Drug product specifications include: appearance, identification by HPLC and IR, assay by HPLC, related substances by HPLC, uniformity of content USP, water content by Karl Fischer, residual solvents by GC, dissolution and disintegration. Reference standard certificates of analysis are provided for the API, fexofenadine HCl, and ~~_____~~

b(4)

Although somewhat heavier than most orally disintegrating tablets, Allegra ODT 30 mg tablets are bioequivalent to the marketed 30 mg Allegra tablets and disintegrate in water in 20-30 seconds.

The Allegra ODT 30 mg tablets are supplied in individual aluminum-foil/
blisters sealed with aluminum foil/
, in 6-count cards, packaged into cartons of 10.

b(4)

Adequate stability data were provided to support the proposed expiration dating of 36 months at 25°C (controlled room temperature) for drug product packaged in the selected package configuration (blister cards).

Conclusion: Drug product is satisfactory.

Additional Items:

All associated Drug Master Files (DMFs) are acceptable or the pertinent information has been adequately provided in the application.

A method validation package, describing the test methods and validation procedures, including information supporting the reference standard, is provided. As the analytical methods used in the testing procedures (release and stability) are well known or have been established in previous Allegra submissions, revalidation by Agency laboratories will not be requested.

Overall Conclusion:

From a CMC perspective, the application is recommended for **approval**, pending agreement on product labeling.

Ali Al-Hakim, Ph.D.
Branch Chief, Branch II
DPA I/ONDQA

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NDA 21-909

**Allegra ODT
(fexofenadine HCl)**

sanofi-aventis

**Martin Haber, Ph.D.
Division of Pre-Marketing Assessment 1**

**Review for
Division of Pulmonary and Allergy Drug Products**

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Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	7
I. Recommendations.....	7
A. Recommendation and Conclusion on Approvability	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments.....	7
A. Description of the Drug Product(s) and Drug Substance(s)	7
B. Description of How the Drug Product is Intended to be Used.....	8
C. Basis for Approvability or Not-Approval Recommendation.....	8
III. Administrative.....	9
A. Reviewer's Signature.....	9
B. Endorsement Block.....	9
C. CC Block	9
Chemistry Assessment	10
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	10
S DRUG SUBSTANCE [fexofenadine HCl, sanofi-aventis]	10
P DRUG PRODUCT [Allegra ODT, sanofi-aventis]	10
A APPENDICES	18
R REGIONAL INFORMATION	18
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	18
A. Labeling & Package Insert	18
B. Environmental Assessment Or Claim Of Categorical Exclusion	18
III. List Of Deficiencies To Be Communicated.....	18



Chemistry Review Data Sheet

1. NDA 21-909
2. REVIEW #2
3. REVIEW DATE: June 4, 2007
4. REVIEWER: Martin Haber, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Pre-NDA Mtg	3/8/05
Original electronic NDA	9/28/06
e-Amendment	1/18/07
e-Amendment	2/8/07

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
e-Amendment	5/7/07

7. NAME & ADDRESS OF APPLICANT:

Name: sanofi-aventis

Address: 200 Crossing Blvd, PO Box 6890, Bridgewater, NJ 08897

Representative: Dr. Lori Birkenberger, Associate Director, Regulatory Development

Telephone: (908) 231-3126

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
					N/A	N/A	Low risk, no review needed
						N/A	Low risk, no review needed
						N/A	Low risk, no review needed
					ate	4/19/05	Reviewed by Dr. Craig Bertha
					ate	2/10/05	Low risk, GRAS, no review needed
					quate	3/29/07	Low risk, GRAS, reviewed by this reviewer

b(4)

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

b(4)

2 – _____

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")



CHEMISTRY REVIEW



Chemistry Review Data Sheet

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	62,912	Allegra Flashtabs

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	All sites are acceptable	11/2/06	
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A		
DMETS	Acceptable	3/21/07	L. Pincock
EA	FONSI	4/29/07	R. Bloom
Microbiology	N/A		

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The Chemistry Review for NDA 21-909

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend Approval

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance

Allegra ODT (orally disintegrating tablet) is indicated for treatment of seasonal allergic rhinitis and chronic idiopathic urticaria in children. Allegra ODT (fexofenadine HCl) is an immediate release orally disintegrating tablet intended for twice-a-day oral dosing. Each Allegra ODT is a white, flat-faced, 1/2-in round shaped tablet that is debossed with a scripted "e" symbol on one side and "311AV" on the other side. The total tablet weight is _____

b(4)

Each tablet contains 30 mg of the active ingredient, fexofenadine HCl, _____ with methacrylate copolymer _____ the excipients microcrystalline cellulose, sodium starch glycolate, povidone K-30 and magnesium stearate. _____

b(4)

_____ citric acid anhydrous, crospovidone, magnesium stearate, mannitol, microcrystalline cellulose, sodium bicarbonate, aspartame, natural and artificial orange flavor, artificial cream flavor, and _____ alcohol anhydrous (which is predominantly removed during manufacturing). Due to its bitter taste, the active ingredient is taste-masked inside the _____. The _____ dissolves in the stomach at acid pH and the active is released. Flavorings and sweetener are added to make the disintegrating tablet pleasant tasting.

b(4)

b(4)

The drug product orally disintegrating tablets are manufactured at CIMA LABS INC.'s facility in Eden Prairie, MN using their proprietary OraSolv® technology. Critical aspects of the process include; _____

b(4)

_____ Drug product

Executive Summary Section

specifications include: identification, assay, related substances, uniformity of content, water content, residual solvents, dissolution and disintegration. The drug product container/closure system is an individual aluminum-foil/aluminum foil blister, in 6-count cards, packaged into cartons of 10. Drug product tablets in this container/closure have been demonstrated to be stable for _____ at controlled room temperature. b(4)

Fexofenadine hydrochloride is a non-sedating, long-acting anti-histamine with selective peripheral histamine H1-receptor antagonist activity. Both enantiomers are equipotent. All chemistry information on the drug substance is provided by cross-reference to NDA 20-625 for Allegra Capsules (approved 7/25/96) from the same sponsor, sanofi-aventis, and all subsequent supplements and annual reports made thereto. No new information on the drug substance is provided in the reviewed NDA. Although there are two approved manufacturers, only drug substance manufactured from Aventis' Frankfurt, Germany facility will be used for the ODT product. There is no USP monograph. Other NDAs, NDA 20-872 (approved 2/25/00) for Allegra Tablets, NDA 21-963 (approved 10/16/06) for Allegra Oral Suspension, and the Allegra-D formulations (NDA's 21-704 and 20-786), all from the same sponsor, sanofi-aventis, also use the same drug substance with the same controls.

B. Description of How the Drug Product is Intended to be Used

Allegra ODT is indicated for relief of symptoms associated with seasonal allergic rhinitis and chronic idiopathic urticaria (itchy rash) in children 6 to 11 years of age. The recommended dose is 30 mg, twice daily. Allegra ODT should be allowed to disintegrate into small particles on the tongue, followed by swallowing with or without water (water only, not juice). Allegra ODT is not intended to be chewed since that would release the bitter active ingredient. Tablets should be taken on an empty stomach because when taken with a high-fat meal the bioavailability of fexofenadine HCl decreases significantly. Although somewhat heavier than most ODT's at a tablet weight of _____ Allegra ODT 30 mg tablets are bioequivalent to the marketed 30 mg Allegra tablets and disintegrate in water in 20-30 seconds. b(4)

C. Basis for Approvability or Not-Approval Recommendation

The chemistry information provided for the drug product is now adequate, since the applicant has submitted a satisfactory reply to the Agency's chemistry comments on the drug product regarding the in-process specification for _____ particle size, the _____ excipient description, the dissolution test method and limits on impurities (the response is covered in this review). No new information on drug substance is provided in this NDA. The cGMP status of all manufacturing facilities is satisfactory as per EER on 11/2/06. The EA review resulted in a Finding Of No Significant Impact (FONSI) on 4/29/07. b(4)

III. Administrative

A. Reviewer's Signature

See DFS

B. Endorsement Block

See DFS

C. CC Block

See DFS

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Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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Ali Al-Hakim
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OND Division of Pulmonary and Allergy Products

NDA: 21-909

Applicant: Sanofi-Aventis

Stamp Date: 29-Sep-2006

PDUFA Date: 29-Jul-2007

ONDQA 4 month date: 29-Jan-2007

Proposed Proprietary Name: Allegra® Orally Disintegrating Tablets

Established Name: (fexofenadine hydrochloride)

Dosage form and strength: Orally Disintegrating Tablets (30 mg per tablet).

Route of Administration: oral

Indications: seasonal allergic rhinitis (SAR) and chronic idiopathic urticaria (CIU)

PAL: Prasad Peri, Ph.D. Branch II/DPA I/ONDQA

Fileability recommendation: Acceptable for filing

Review team recommendation: Single primary reviewer (Martin Haber, Ph.D)

Time goals:

- **Initial Quality Assessment in DFS: by 29-Oct-2006** (tentative by 23-Sep-2006)
- **Chemistry filing memo in DFS: by 17-Nov-2006** (tentative by 29-Oct-2006)
- Filing decision "Day 45": 17-Nov-2006 (tentative; to be set by Clinical Division)
- Filing review issues "Day 74": 14-Dec-2006 (tentative; to be set by Clinical Division)
- **Chemistry Review (DR/IR) letter: by 28-Feb-2007**
- Mid-cycle meeting "Month 5": 28-Feb-2007 (tentative)
- Wrap Up: 20-May-2007
- **Final Chemistry Review "Month 8" in DFS: by 29-May-2007**
- PDUFA: 29-Jul-2007

IND 43,573 fexofenadine HCl	DMF #
IND 62,912 fexofenadine HCl, orally disintegrating tablet	DMF #
IND 51,709 fexofenadine HCl pediatric formulation	DMF #
NDA 20-625 ALLEGRA® (fexofenadine HCl) capsules	DMF #
NDA 20-872 ALLEGRA® (fexofenadine HCl) tablets	DMF #

b(4)

b(4)

CONSULTS/ CMC RELATED REVIEWS	COMMENT
Biopharm/ClinPharm	To be determined by Primary Reviewer
CDRH	<i>Not Applicable</i>
EA	Exclusion requested. Certification provided.
EES	EER sent to Office of Compliance on 10-Oct-2006. All sites OK
DMETS	<i>Labeling consult request will be sent as part of DPAP's request.</i>
Methods Validation	<i>Validation may be requested of FDA labs after test methods are finalized.</i>
Microbiology	<i>May be necessary as moisture content ranges from 4-6%</i>
Pharm/Tox	<i>DS and DP Impurities to be qualified</i>
Labeling and Nomenclature	<i>Note the USAN name should be applied for. The established name needs to be checked for accuracy.</i>

Summary:

- This is a standard (10 month) electronic/ NDA in CTD format with electronic labeling provided in SPL format. There is a Chemistry Quality Overall Summary (~90 pages). This NDA is filed as a 505(b)(2) application. The associated IND is IND 62,912 (fexofenadine HCl, 180 mg, orally disintegrating tablets originally called flashtabs, originally reviewed by Dr. Brian Rogers).
- On 10-Jan-2003, there was an EoP2 meeting with Aventis that indicated the Agency's concern for the size of the tablet ~~_____~~ and also the proposed disintegration and dissolution time of ~~_____~~ of 20-30 minutes. Further comments on OVI's, extant of stability information, and nomenclature of the tablet were made by the Agency. The Agency stated that hardness and friability should be specified at release and stability and if not, they should address the robustness of the product during manufacturing, packaging and shipping.
- Similar comments regarding tablet weight, disintegration time and nomenclature were provided in the preNDA meeting with the applicant held March 5, 2005. In addition, comments on hold time for the bulk ~~_____~~ and tablets and their relevance to the shelf life of the product were discussed.
- During drug development the formulation was optimized to address low dissolution properties resulting in a failed initial pilot PK study (H1130). Formulation was optimized in terms of total amount of fexofenadine used in the ~~_____~~ (reduction from ~~_____~~ ~~_____~~, change from using ~~_____~~ to alcohol as the ~~_____~~. The tablet size and weight were also ~~_____~~ from the initial tablet formulas (~~_____~~ and ~~_____~~ in diameter and ~~_____~~ in weight. The composition of the clinical trial batches used in exploratory relative bioavailability/pharmacokinetic study (H10004) and batches used in pivotal clinical study (h10007) are provided at the end of this assessment.
- The development process described in the CMC summary is truly trial and error as opposed to QbD. The disintegration and dissolution acceptance criteria are trend setting and should be evaluated carefully.

b(4)

b(4)

b(4)

Drug Substance

- Since the drug substance is currently approved in several of the Allegra® products, no new information is provided in the submission. It is however noted that one drug substance supplier ~~was~~ was deleted in this submission for this application. The drug substance is manufactured by Sanofi Aventis in Germany. **b(4)**
- Chemistry, manufacturing, and controls information on the drug substance fexofenadine HCl is provided by cross-reference to the approved NDA 20-625 for Allegra Capsules (submitted July 31, 1995, approved July 25, 1996) and all subsequent supplements and Annual Reports made thereto.
- For the convenience of the reviewer, the present table (Table 1 (pages 5-13)) provides an index of all approved CMC supplements and Annual Report submissions to NDA 20-625 for Allegra Capsules. This table identifies the NDA sections of previous supplements or Annual Reports where relevant CMC information on the fexofenadine HCl drug substance can be found. See specifications for the bulk API at the end of this assessment.
- The drug substance specifications include Description, Powder fineness, Specific Surface Area, Specific Rotation, DSC, ID by IR and HPLC, Water Content, Assay (HPLC), Related Substances, Residual Solvents, Heavy metals, Chloride content, and Residue on Ignition. Note that the list and acceptance criteria are reproduced at the end of this assessment. Only one impurity ~~at~~ is specified above the ICH Q3A(R) qualification limit. The reviewer needs to send in a consult to evaluate their proposed limits for safety. **b(4)**
- No information on the container closure and stability for drug substance is provided in this NDA.

Drug Product

- Fexofenadine Orally Disintegrating tablets are white, flat-faced 1/2" round, beveled edge tablet with "" on one side and "311 AV" on the other side. They contain 30 mg of the active and at a total weight of ~~_____~~. They are designed to break up in the oral cavity upon contact with the saliva with the resultant ~~_____~~ then being swallowed to allow rapid presentation of the drug for absorption ~~_____~~ batches using ~~_____~~ of the final blend produces a theoretical amount of ~~_____~~ each. **b(4)**
- The Fexofenadine HCl Orally Disintegrating Tablet, 30 mg formulation is based on CIMA LABS INC. proprietary OraSolv® technology. The formulation is designed to be made in ~~_____~~ **b(4)**
- The ~~_____~~ p is the ~~_____~~ the ~~_____~~ involved ~~_____~~ **b(4)**
- Note that the ~~_____~~ that goes into the ~~_____~~ process ~~_____~~ contains ~~_____~~ of ~~_____~~ which is equivalent to 30 mg of fexofenadine HCl. The process of manufacture is relatively different compared to a standard ~~_____~~ tablet. **b(4)**

ONDQA PAL's Initial Quality Assessment
Prasad Peri, Ph.D., Division of Pre-Marketing Assessment 1, Branch 2

Table 1 - Composition of Fexofenadine HCl Orally Disintegrating Tablets, 30 mg

COMPONENTS	COMPOSITION		FUNCTION	REFERENCE TO STANDARDS (2)
	Proportion (% w/w)	Per Unit (mg)		
Fexofenadine HCl			Active Substance	Aventis
Microcrystalline Cellulose				USP/NF
Sodium Starch Glycolate				USP/NF
Povidone K-30				USP/NF
				Ph. Eur./JPE ¹
Magnesium Stearate				USP/NF ²
Alcohol, Anhydrous				CIMA ³
Total				
Fexofenadine HCl			Active Substance	CIMA
Mannitol ⁵				USP/NF
Mannitol ⁵				USP/NF
Crospovidone				USP/NF
Microcrystalline Cellulose ⁶				USP/NF
Sodium Bicarbonate, No. 1				USP/NF
Citric Acid, Anhydrous				USP/NF
Aspartame				USP/NF
Magnesium Stearate				USP/NF
Natural and Artificial Orange Flavor				GRAS ⁷
Artificial Cream Flavor				GRAS ⁷
Total				

b(4) 1. At the time of manufacture the [redacted] was tested as per the DAB(Deutsches Arzneibuch)/JPE compendial requirements. Since then the Ph. Eur. has added a monograph for [redacted] in the future, this excipient will be tested according to the Ph. Eur./JPE specifications.

b(4) 2. [redacted]

b(4) 3. Substituted alcohol as per USP. Complies to USP for ethyl alcohol content. The alcohol [redacted] is a non-compendial excipient. Alcohol is a [redacted] (volume/volume), which conforms to 27 CFR 21.35

b(4) 4. Removed during processing.

b(4) 5. Amount adjusted based on the assay of the [redacted] fexofenadine HCl [redacted]

6. [redacted] microcrystalline cellulose is used for tablet manufacture.

7. Generally Recognized as Safe (GRAS).

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Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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Blair Fraser
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NDA 21-909

**Allegra ODT
(fexofenadine HCl)**

sanofi-aventis

**Martin Haber, Ph.D.
Division of Pre-Marketing Assessment 1**

**Consult Review for
Division of Pulmonary and Allergy Drug Products**

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Table of Contents

Table of Contents	2
Chemistry Review Data Sheet	3
The Executive Summary	7
I. Recommendations.....	7
A. Recommendation and Conclusion on Approvability	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments.....	7
A. Description of the Drug Product(s) and Drug Substance(s)	7
B. Description of How the Drug Product is Intended to be Used.....	8
C. Basis for Approvability or Not-Approval Recommendation.....	8
III. Administrative.....	9
A. Reviewer's Signature.....	9
B. Endorsement Block.....	9
C. CC Block	9
Chemistry Assessment	10
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	10
S DRUG SUBSTANCE [fexofenadine HCl, sanofi-aventis]	10
P DRUG PRODUCT [Allegra ODT, sanofi-aventis]	14
A APPENDICES	59
R REGIONAL INFORMATION	59
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	59
A. Labeling & Package Insert	59
B. Environmental Assessment Or Claim Of Categorical Exclusion	63
III. List Of Deficiencies To Be Communicated.....	64



Chemistry Review Data Sheet

1. NDA 21-909
2. REVIEW #1
3. REVIEW DATE: April 9, 2007
4. REVIEWER: Martin Haber, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Pre-NDA Mtg	3/8/05

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original electronic NDA	9/28/06
Amendment	1/18/07
Amendment	2/8/07

7. NAME & ADDRESS OF APPLICANT:

Name: sanofi-aventis

Address: 200 Crossing Blvd, PO Box 6890, Bridgewater, NJ 08897

Representative: Dr. Lori Birkenberger, Associate Director, Regulatory Development

Telephone: (908) 231-3126

8. DRUG PRODUCT NAME/CODE/TYPE:



CHEMISTRY REVIEW



Chemistry Review Data Sheet

- a) Proprietary Name: **Allegra ODT**
- b) Non-Proprietary Name (USAN): fexofenadine HCl
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3 (new formulation)
 - Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Anti-histamine

11. DOSAGE FORM: Tablet, orally disintegrating

12. STRENGTH/POTENCY: 30 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

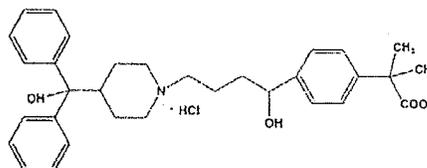
Name: Benzeneacetic acid, 4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidiny]butyl]- α,α -dimethyl-, hydrochloride. (\pm)

Mol Formula: $C_{32}H_{39}NO_4 \cdot HCl$

Mol Weight: 538.12

CAS Reg No: HCl Salt:[138452-21-8]

Base :[83799-24-0]



(USAN 2000, p 302)

b(4)



CHEMISTRY REVIEW



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
					N/A	N/A	Low risk, no review needed
					A	N/A	Low risk, no review needed
						N/A	Low risk, no review needed
					adequate	4/19/05	Reviewed by Dr. Craig Bertha
					adequate	2/10/05	Low risk, GRAS, no review needed
					adequate	3/29/07	Low risk, GRAS, reviewed by this reviewer

b(4)

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

b(4)

2 _____

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")



CHEMISTRY REVIEW



Chemistry Review Data Sheet

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	62,912	Allegra Flashtabs

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	All sites are acceptable	11/2/06	
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A		
DMETS	AC	3/21/07	L. Pincock
EA	Pending		
Microbiology	N/A		

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The Chemistry Review for NDA 21-909

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend Approval, pending a satisfactory response to chemistry comments (see last page).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Allegra ODT is indicated for treatment of seasonal allergic rhinitis and chronic idiopathic urticaria in children 6 to 11 years of age. Allegra ODT (fexofenadine HCl) is an immediate release orally disintegrating tablet intended for twice-a-day oral dosing. Each Allegra ODT is a white, flat-faced, 1/2-in round shaped tablet that is debossed with a scripted "e" symbol on one side and "311AV" on the other side. The total tablet weight is ~~_____~~. Each tablet contains 30 mg of the active ingredient, fexofenadine HCl.

b(4)

~~_____~~ alcohol anhydrous (which is predominantly removed during manufacturing). Due to its bitter taste, the active ingredient is taste-masked inside the ~~_____~~ and released in the stomach at acid pH. Flavorings and sweetener are added to make the disintegrating tablet pleasant tasting.

b(4)

The drug product orally disintegrating tablets are manufactured at CIMA LABS INC.'s facility in Eden Prairie, MN using their proprietary OraSolv® technology. Critical aspects of the manufacturing process include for ~~_____~~

b(4)

~~_____~~ Drug product specifications include: identification, assay, related substances, uniformity of content, water content, residual solvents, dissolution and

CHEMISTRY REVIEW

Executive Summary Section

disintegration. The drug product container/closure system is an individual aluminum-foil/aluminum foil blister, in 6-count cards, packaged into cartons of 10. Drug product tablets in this container/closure have been demonstrated to be stable for _____ at controlled room temperature. b(4)

Fexofenadine hydrochloride is a non-sedating, long-acting anti-histamine with selective peripheral histamine H1-receptor antagonist activity. Both enantiomers are equipotent. All chemistry information on the drug substance is provided by cross-reference to NDA 20-625 for Allegra Capsules (approved 7/25/96) from the same sponsor, sanofi-aventis, and all subsequent supplements and annual reports made thereto. No new information on the drug substance is provided in this NDA, NDA 21-909. Although there are two approved manufacturers, only drug substance manufactured from Aventis' Frankfurt, Germany facility will be used for the ODT product. There is no USP monograph. Other NDAs, NDA 20-872 (approved 2/25/00) for Allegra Tablets, NDA 21-963 (approved 10/16/06) for Allegra Oral Suspension, and the Allegra-D formulations (NDA's 21-704 and 20-786), all from the same sponsor, sanofi-aventis, also use the same drug substance with the same controls.

B. Description of How the Drug Product is Intended to be Used

Allegra ODT is indicated for relief of symptoms associated with seasonal allergic rhinitis and chronic idiopathic urticaria in children 6 to 11 years of age. The recommended dose is 30 mg, twice daily. Allegra ODT should be allowed to disintegrate into small particles on the tongue, followed by swallowing with or without water (water only, not juice). Allegra ODT is not intended to be chewed since that would release the bitter active ingredient. Tablets should be taken on an empty stomach because when taken with a high-fat meal the bioavailability of fexofenadine HCl decreases significantly. Although somewhat bigger than most ODT's at a tablet weight of _____, Allegra ODT 30 mg tablets are bioequivalent to the 30 mg Allegra tablets and disintegrate in water in about 20-30 seconds. b(4)

C. Basis for Approvability or Not-Approval Recommendation

The chemistry information provided for the drug product should be adequate, pending a satisfactory reply to comments sent to the applicant. Chemical manufacturing, controls, and quality testing for the drug product are adequate except for an in-process specification for _____ particle size, an excipient description, a dissolution test method description and limits on impurities. No new information on drug substance is provided in this NDA. The cGMP status of all manufacturing facilities is satisfactory as per EER on 11/2/06. An EA is pending. b(4)



III. Administrative

A. Reviewer's Signature

See DFS

B. Endorsement Block

See DFS

C. CC Block

See DFS

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55 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/

Martin Haber
4/16/2007 02:54:20 PM
CHEMIST
See last page for chemistry comments

Blair Fraser
4/17/2007 11:51:16 AM
CHEMIST

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DEPARTMENT OF HEALTH AND HUMAN SERVICES Food and Drug Administration			REQUEST FOR CONSULTATION	
TO (Division/Office) OPS/PARS			FROM ONDQA/DPA-1	
DATE 1/24/2007	IDA NO.	NDA NO. 21-909	TYPE OF DOCUMENT Electronic	DATE OF DOCUMENT 9/28/2006
NAME OF DRUG Allegra ODT		PRIORITY CONSIDERATION S	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE 3/28/2007
NAME OF FIRM Sanofi-aventis				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL	<input type="checkbox"/> PRE-NDA	<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER		
<input type="checkbox"/> PROGRESS REPORT	<input type="checkbox"/> END OF PHASE II MEETING	<input type="checkbox"/> FINAL PRINTED LABELING		
<input type="checkbox"/> NEW CORRESPONDENCE	<input type="checkbox"/> RESUBMISSION	<input type="checkbox"/> LABELING REVISION		
<input type="checkbox"/> DRUG ADVERTISING	<input type="checkbox"/> SAFETY/EFFICACY	<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE		
<input type="checkbox"/> ADVERSE REACTION REPORT	<input type="checkbox"/> PAPER NDA	<input type="checkbox"/> FORMULATIVE REVIEW		
<input type="checkbox"/> PMANUFACTURING CHANGE/ADDITION	<input type="checkbox"/> CONTROL SUPPLEMENT	<input checked="" type="checkbox"/> OTHER (Specify below)		
<input type="checkbox"/> MEETING PLANNED BY <u>kljsgkl</u>		<u>Environmental Assessment</u>		
II. BIOMETRICS				
STATISTICAL EVALUATION		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW		<input type="checkbox"/> CHEMISTRY		
<input type="checkbox"/> END OF PHASE II MEETING		<input type="checkbox"/> PHARMACOLOGY		
<input type="checkbox"/> CONTROLLED STUDIES		<input type="checkbox"/> BIOPHARMACEUTICS		
<input type="checkbox"/> PROTOCOL REVIEW		<input type="checkbox"/> OTHER _____		
<input type="checkbox"/> OTHER _____				
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE		
<input type="checkbox"/> BIOAVAILABILITY STUDIES		<input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS		
<input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY		
<input type="checkbox"/> DRUG USE E.G. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES		<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE		
<input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below in comments)		<input type="checkbox"/> POISON RISK ANALYSIS		
<input type="checkbox"/> COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP				
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS (Attach additional sheets if necessary)				
Attention: Bai Nguyen, OPS cc: Raanan Bloom, OPS Please review EA				
SIGNATURE OF REQUESTER		METHOD OF DELIVERY (Check One)		
		<input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERY		

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/s/

Martin Haber
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